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Health and Environmental Effects
Profile for Paraldehyde

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR PARALDEHYDE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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16. ABSTRACT The Health and Environmental Effects Profile for Paraldehyde was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine a Reference Dose (RfD) or a carcinogenic potency factor for <u>paraldehyde</u>. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for <u>paraldehyde</u> is 1000.			
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA and CERCLA dockets.

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EXECUTIVE SUMMARY

Paraldehyde is a clear, colorless liquid at room temperature (U.S. EPA-NIH, 1985). The U.S. EPA TSCA Inventory (U.S. EPA, 1977) lists Union Carbide in Institute, WV, as a manufacturer and Lonza, Inc. as an importer. No production data were reported, and import data were confidential. Paraldehyde can be made by the addition of mineral acid to acetaldehyde or may be continuously formed by feeding acetaldehyde over an acid ion-exchange resin (Persak and Blair, 1978). Paraldehyde is used primarily as a medicine (U.S. EPA, 1980) but is also used as a substitute for acetaldehyde, as rubber accelerators and antioxidants, to make synthetic organic chemicals, as a dyestuff intermediate, as a solvent for fats, oils, waxes, gums, resins and leather, and in solvent mixtures for cellulose derivatives (Hawley, 1981).

Hawley (1981) reported that paraldehyde decomposes on standing, but lack of sufficient information precluded determining the mechanisms used and the extent of decomposition.

Pertinent data regarding the reaction of paraldehyde with $\text{HO}\cdot$ indicates that this is not an important degradation mechanism. Based on vapor pressure and WS data, volatilization of paraldehyde from shallow waters is predicted to be significant, and possibly significant but not rapid from deeper waters (Lyman et al., 1982). Bioaccumulation in aquatic organisms is unlikely.

In the atmosphere, a $\text{HO}\cdot$ reaction half-life of 4-6 days has been estimated from a correlation to aquatic $\text{HO}\cdot$ reaction data (Guesten et al. 1981). Pertinent data regarding the reactions and removal processes of paraldehyde in air and soil could not be located in the available literature.

Pertinent data regarding the presence of paraldehyde in water, air, food or soil could not be located in the available literature as cited in the Appendix. Paraldehyde has been identified in the leachate of two waste disposal sites (Francis et al., 1980). Since paraldehyde is used as a drug, it may have entered the leachate from hospital wastes found at these sites (Francis et al., 1980). The lack of monitoring data may be explained by the fact that paraldehyde decomposes on standing (Hawley, 1981). Furthermore, since paraldehyde is used primarily as a medicine, environmental contamination is not likely to occur (U.S. EPA, 1980). Possible sources of contamination include production, and processing and use facilities (perhaps associated with the pharmaceutical industry).

Pertinent data regarding effects of paraldehyde on aquatic biota could not be located in the available literature as cited in the Appendix.

Orally administered paraldehyde is rapidly absorbed by the gastrointestinal tract (Osol and Pratt, 1973). In humans, the oral administration resulted in 93% absorption (Anthony, 1980).

Paraldehyde is rapidly distributed to the brain within 2-5 seconds after intravenous injection, causing drowsiness (Gardner and Sage, 1941; Robinson, 1938). Paraldehyde can cross the placental barrier (Kotz and Kaufman, 1939; Goodman and Gilman, 1970).

Of the administered paraldehyde ~70-80% is metabolized in the liver (Levine et al., 1939; Hitchcock and Nelson, 1943; Keplinger and Wells, 1957; Breen et al., 1973; Browne, 1983; Goodman and Gilman, 1970). In the liver, paraldehyde depolymerizes to acetaldehyde by cytochrome P-450 mixed function oxidase. Acetaldehyde is then oxidized by aldehyde hydrogenase to acetic acid, which is metabolized to carbon dioxide and water (Hitchcock and Nelson, 1943; Goodman and Gilman, 1970; Zera and Nagasawa, 1981; Zaleska and Gessner, 1983a,b).

The excretion of paraldehyde through the exhaled air as a parent compound ranges from 7-9.6% in humans, cats and mice (Lang and Borgstedt, 1969; Levine et al., 1940; Lang and Borgstedt, 1968; Zaleska and Gassner, 1983b) and up to 28% in dogs (Levine et al., 1940). No other exhaled products were detected. Of administered paraldehyde, 3% was detected in the urine of dogs and mice (Levine et al., 1940; Zaleska and Gassner, 1983b).

Paraldehyde was negative as a tumor initiator when applied to the skin of mice followed by promotion with croton oil (Row and Salaman, 1955). Paraldehyde was also negative in a reverse mutation assay in S. typhimurium strains TA100 and TA98 with and without metabolic activation (Sasaki and Endo, 1978). Pertinent data regarding the teratogenicity and reproductive effects in laboratory animals could not be located in the available literature as cited in the Appendix. Therapeutic administration of paraldehyde to human mothers during labor has resulted in delayed respiratory movements in neonates (Goodman and Gilman, 1970). No chronic or subchronic toxicity studies in laboratory animals were available. Paraldehyde is used therapeutically in humans as a depressant at oral doses of 5-10 mL (~5-10 g) (Goodman and Gilman, 1970). Prolonged use results in tolerance and dependence, acidosis, bleeding gastritis, muscular irritability, fatty changes in the liver and kidney, hepatitis, nephrosis, pulmonary hemorrhage and dilation of the right heart, among other effects. Withdrawal may result in delirium tremens. Deaths have occurred at doses of 25-150 g. At acute doses slightly higher than 8 mL (~8 g), labored breathing and hypotension result. The manifestations of acute poisoning are similar to those of chronic poisoning.

Data were insufficient to derive a q_1^* , ADI or F factor. Paraldehyde is an IARC Group 3 chemical. Based on U.S. EPA (1984) guidelines for carcinogen risk assessment, lack of evidence for human carcinogenicity and inadequate evidence for animal carcinogenicity, paraldehyde is classified as Group D. An RQ of 1000 was derived based on the effects of prolonged therapeutic use of paraldehyde in humans.

TABLE OF CONTENTS

	<u>Page</u>
1. INTRODUCTION.	1
1.1. STRUCTURE AND CAS NUMBER	1
1.2. PHYSICAL AND CHEMICAL PROPERTIES	1
1.3. PRODUCTION DATA.	2
1.4. USE DATA	2
1.5. SUMMARY.	2
2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES.	4
2.1. WATER.	4
2.1.1. Hydrolysis.	4
2.1.2. Oxidation	4
2.1.3. Microbial Degradation	4
2.1.4. Volatilization.	5
2.1.5. Adsorption.	5
2.1.6. Bioaccumulation	5
2.2. AIR.	5
2.3. SOIL	6
2.4. SUMMARY.	6
3. EXPOSURE.	8
3.1. WATER.	8
3.2. AIR.	8
3.3. FOOD	8
3.4. DERMAL	9
3.5. SUMMARY.	9
4. PHARMACOKINETICS	10
4.1. ABSORPTION	10
4.2. DISTRIBUTION	10
4.3. METABOLISM	10
4.4. EXCRETION.	12
4.5. SUMMARY.	12
5. EFFECTS	14
5.1. CARCINOGENICITY.	14
5.2. MUTAGENICITY	14
5.3. TERATOGENICITY	14
5.4. OTHER REPRODUCTIVE EFFECTS	14
5.5. CHRONIC AND SUBCHRONIC TOXICITY.	15
5.6. OTHER RELEVANT INFORMATION	15
5.7. SUMMARY.	16

TABLE OF CONTENTS (cont.)

	<u>Page</u>
6. AQUATIC TOXICITY.	17
7. EXISTING GUIDELINES AND STANDARDS	18
7.1. HUMAN.	18
7.2. AQUATIC.	18
8. RISK ASSESSMENT	19
9. REPORTABLE QUANTITIES	20
9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY	20
9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY.	20
10. REFERENCES.	22
APPENDIX: LITERATURE SEARCHED.	29

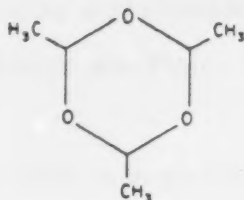
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
K _{oc}	Soil sorption coefficient standardized with respect to organic carbon
K _{ow}	Octanol/water partition coefficient
LD ₅₀	Dose lethal to 50% of recipients
MED	Minimum effective dose
ppm	Parts per million
RQ	Reportable quantity
RV _d	Dose-rating value
RV _e	Effect-rating value
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Paraldehyde is also known as 2,4,6-trimethyl-1,3,5-trioxane, para-acetaldehyde, acetaldehyde trimer and s-trimethyltrioxymethylene. The structure, molecular weight, chemical formula and CAS Registry number for paraldehyde are as follows:



Molecular weight: 132.2

Chemical formula: $C_6H_{12}O$

CAS Registry number: 123-63-7

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Paraldehyde is a clear, colorless liquid at room temperature (U.S. EPA-NIH, 1985). Its odor has been reported to be offensive (Stedman's, 1982), agreeable (Hawley, 1981) and characteristically aromatic (Windholz, 1983) and its taste is reportedly warm, but disagreeable (Windholz, 1983). Selected physical properties are listed below:

Melting point:	12.6°C	Hawley, 1981
Boiling point:	124.5°C	Hawley, 1981
Vapor pressure (at 20°C):	25.5 mm Hg	Weber et al., 1981
Water solubility (at 25°C):	1.25×10^3 ppm	Windholz, 1983
Log K_{ow} :	0.67	Hansch and Leo, 1985
Specific gravity (20°C/20°C):	0.9960	Hawley, 1981
Flash point:	35.5°C	Hawley, 1981

1.3. PRODUCTION DATA

The U.S. EPA TSCA Inventory (U.S. EPA, 1977) lists Union Carbide in Institute, WV, as a manufacturer of paraldehyde, although none was produced in 1977. Lonza, Inc. is listed as an importer, but the import data were confidential. Paraldehyde is formed when a mineral acid, such as sulfuric, phosphoric or hydrochloric acid, is added to acetaldehyde. Paraldehyde can be formed continuously by feeding acetaldehyde as a liquid (at 15-20°C) over an acid ion-exchange resin (Persak and Blair, 1978).

1.4. USE DATA

Paraldehyde is primarily used in medicine (U.S. EPA, 1980) as a depressant drug, which may be addictive (Hawley, 1981). It is a hypnotic sedative used to treat delirium tremens, for long-term treatment of psychiatric states characterized by excitement, for intractable pain not responsive to opiates, as basal and obstetrical anesthesia, and in emergency treatment of convulsions (U.S. EPA, 1980). It is also used as a substitute for acetaldehyde, as rubber accelerators and antioxidants, to make synthetic organic chemicals, as a dyestuff intermediate, as a solvent for fats, oils, waxes, gums, resins and leather, and in solvent mixtures for cellulose derivatives (Hawley, 1981).

1.5. SUMMARY

Paraldehyde is a clear, colorless liquid at room temperature (U.S. EPA-NIH, 1985). The U.S. EPA TSCA Inventory (U.S. EPA, 1977) lists Union Carbide in Institute, WV, as a manufacturer and Lonza, Inc. as an importer. No production data were reported and import data were confidential. Paraldehyde can be made by the addition of mineral acid to acetaldehyde or may be formed continuously by feeding acetaldehyde over an acid ion-exchange resin

(Persak and Blair, 1978). Paraldehyde is primarily used as a medicine (U.S. EPA, 1980) but is also used as a substitute for acetaldehyde, as rubber accelerators and antioxidants, to make synthetic organic chemicals, as a dyestuff intermediate, as a solvent for fats, oils, waxes, gums, resins and leather, and in solvent mixtures for cellulose derivatives (Hawley, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Hawley (1981) reported that paraldehyde decomposes on standing, but no further information was provided. U.S. EPA-NIH (1985) reported a first-order rate constant of 0.012 day^{-1} for the bacterial and chemical degradation of paraldehyde. Additional data are necessary before the significance of this information can be determined.

2.1. WATER

2.1.1. Hydrolysis. Pertinent data regarding the hydrolysis of paraldehyde could not be located in the available literature as cited in the Appendix.

2.1.2. Oxidation. The rate constant for the reaction between paraldehyde and $\text{HO}\cdot$ at room temperature has been reported to be $6.0 \times 10^9 \text{ M}^{-1} \text{ sec}^{-1}$ (Anbar and Neta, 1967) and $1.0 \times 10^9 \text{ M}^{-1} \text{ sec}^{-1}$ (Dorfman and Adams, 1973). Using an aquatic $\text{HO}\cdot$ concentration of 10^{-17} M (Mill et al., 1980), the half-life can be estimated to be >2 years, indicating that this reaction has no environmental significance.

Pertinent data regarding the aquatic reaction between paraldehyde and singlet oxygen or RO_2 in water could not be located in the available literature as cited in the Appendix.

2.1.3. Microbial Degradation. Results of the MITI test classify paraldehyde as a compound resistant to degradation (Kawasaki, 1980). This means $<30\%$ of a sample incubated with activated sludge was degraded in 14 days (Sasaki, 1978). A bacterium isolated from sewage, *C. paraldehydium* KY 4359, has been known to degrade paraldehyde to acetaldehyde and acetic acid under specific laboratory conditions (Takayama et al., 1970).

2.1.4. Volatilization. Pertinent data regarding the volatilization of paraldehyde in water were not located; however, prediction of the likelihood of volatilization can be made from vapor pressure and WS data. A Henry's Law constant was calculated to be 3.55×10^{-5} atm·m³/mol from the following equation (Lyman et al., 1982):

$$H = P_{vp}(\text{atm})/WS (\text{mol/m}^3)$$

using a WS of 125,000 ppm at 25°C (Windholz, 1983) and a vapor pressure of 25.5 mm Hg at 20°C (Weber et al., 1981). A Henry's Law constant of this magnitude indicates that volatilization from shallow waters is significant and evaporation from deeper waters may be significant although not rapid (Lyman et al., 1982).

2.1.5. Adsorption. Pertinent data regarding adsorption could not be located in the available literature as cited in the Appendix.

2.1.6. Bioaccumulation. Pertinent experimental data regarding bioaccumulation of paraldehyde in aquatic organisms could not be located in the available literature. BCFs were estimated using the following equations: $\log BCF = 0.76 \log K_{ow} - 0.23$ (Veith, 1980) and $\log BCF = 2.791 - 0.564 \log S$ (Lyman et al., 1982). BCF values of 0.82-1.90 were calculated, indicating that bioaccumulation in aquatic organisms is unlikely.

2.2. AIR

Pertinent data regarding the environmental fate and transport of paraldehyde in the atmosphere were not located. Guesten et al. (1981), however, derived a method for estimating the rate constant for the reaction of paraldehyde with HO radicals in the atmosphere from the corresponding rate constant in water. The HO· reaction rate constant in air was determined to be 1.3×10^{-12} and 2.1×10^{-12} cm³ molecule⁻¹ sec⁻¹ (Guesten et al., 1981) from HO· reaction rate constants in water of 6.0×10^8 M⁻¹

sec^{-1} (Anbar and Neta, 1967) and $1.0 \times 10^9 \text{ M}^{-1} \text{ sec}^{-1}$ (Dorfman and Adams, 1973), respectively. Assuming an $\text{HO}\cdot$ concentration of 10^6 molecules/ cm^3 in the atmosphere, a half-life of ~4-6 days can be calculated. Dilling et al. (1976) reported that trioxane, a structural analog of paraldehyde, had a half-life of 4.7 days in the presence of nitric oxide under simulated atmospheric conditions.

2.3. SOIL

Pertinent data regarding the environmental fate and transport of paraldehyde in soil could not be located in the available literature. K_{oc} values can be estimated from the molecular structure (Sabljic, 1984) and WS data (Lyman et al., 1982) to predict whether adsorption to soil is probable. Behavior in soil is likely to depend on more than one physical property; thus, variation in K_{oc} values should be expected depending upon the method of estimation used. Using the method of Sabljic (1984), the K_{oc} for paraldehyde was ~562, indicating low mobility in soil (Swann et al., 1983). Using the equations: $\log K_{oc} = -0.55 \log \text{WS} + 3.64$ (WS in mg/l) and $\log K_{oc} = -0.54 \log \text{WS} + 0.44$ (WS in mol fraction) (Lyman et al., 1982), K_{oc} values were calculated to be 7 and 25, respectively. These values classify paraldehyde as a very mobile compound in soil (Swann et al., 1983). Overall, this information is insufficient for determining whether paraldehyde will adsorb or leach into soil.

2.4. SUMMARY

Hawley (1981) reported that paraldehyde decomposes on standing, but lack of sufficient information precluded determining the mechanisms used and the extent of decomposition.

Pertinent data regarding the reaction of paraldehyde with $\text{HO}\cdot$ in water indicate that this is not an important degradation mechanism. Based on vapor pressure and WS data, volatilization of paraldehyde from shallow waters is predicted to be significant, and possibly significant but not rapid from deeper waters (Lyman et al., 1982). Bioaccumulation in aquatic organisms is unlikely.

In the atmosphere, a $\text{HO}\cdot$ reaction half-life of 4-6 days has been estimated from a correlation to aquatic $\text{HO}\cdot$ reaction data (Guesten et al. 1981). Pertinent data regarding the reactions and removal processes of paraldehyde in air and soil could not be located in the available literature as cited in the Appendix.

3. EXPOSURE

3.1. WATER

The U.S. EPA STORET Data Base (U.S. EPA, 1986) reported no monitoring data on paraldehyde in water. Kool et al. (1982) list the CAS Registry number for paraldehyde in a table identifying compounds found in drinking water, but the name corresponding to this number is not a synonym of paraldehyde. Francis et al. (1980) identified paraldehyde as a constituent of leachate samples from Maxey Flats, KY, and West Valley, NY. Considering the use of this compound as a medicine, paraldehyde could potentially have entered the leachate from hospital wastes found at these sites (Francis et al., 1980).

The lack of monitoring data on paraldehyde in the environment may be due to the decomposition of this compound on standing (Hawley, 1981). Furthermore, since paraldehyde is used mainly as a medicine, the chance of environmental exposure is low (U.S. EPA, 1980). Possible sources of contamination include production, and processing and use facilities (perhaps associated with the pharmaceutical industry).

3.2. AIR

Pertinent monitoring data regarding paraldehyde in the atmosphere could not be located in the available literature as cited in the Appendix.

3.3. FOOD

Hartman and Ho (1982) identified paraldehyde in the volatile component of hydrated collagen heated at normal roasting temperatures. Although the conditions of this study are not the same as actually roasting fresh meat, the compounds identified may possibly be present in cooked meat (Hartman and Ho, 1982).

3.4. DERMAL

Pertinent monitoring data regarding dermal exposure to paraldehyde could not be located in the available literature as cited in the Appendix.

3.5. SUMMARY

Pertinent data regarding the presence of paraldehyde in water, air, food or soil could not be located in the available literature as cited in the Appendix. Paraldehyde has been identified in the leachate of two waste disposal sites (Francis et al., 1980). Since this compound is used as a drug, it may have entered the leachate from hospital wastes found at these sites (Francis et al., 1980). The lack of monitoring data may be explained by the fact that paraldehyde decomposes on standing (Hawley, 1981). Furthermore, since paraldehyde is used primarily as a medicine, environmental contamination is not likely to occur (U.S. EPA, 1980). Possible sources of contamination include production, and processing and use facilities (perhaps associated with the pharmaceutical industry).

4. PHARMACOKINETICS

4.1. ABSORPTION

Paraldehyde is absorbed rapidly from the gastrointestinal tract upon oral administration (Osol and Pratt, 1973). Figot et al. (1952) reported that the maximum concentration in the brain is reached within one-half hour following oral administration in rats. In humans, oral administration resulted in 93% absorption with peak blood levels reached in 20-40 minutes (the dose was not reported) (Anthony, 1980). Anthony et al. (1977) reported that in five ethanol abusers injected intravenously with paraldehyde at 100 mg/kg, followed by equal doses given orally in fruit juice on subsequent days, gastrointestinal absorption was 95%; peak concentrations were reached within 30 minutes.

4.2. DISTRIBUTION

Paraldehyde is rapidly distributed to the brain following an intravenous injection, causing drowsiness within 2-5 seconds and anesthesia in <2 minutes (Gardner and Sage, 1941; Robinson, 1938).

Kotz and Kaufman (1939) reported that paraldehyde can cross the placental barrier.

Levine et al. (1939) gavaged dogs with 1.0-1.5 mL/kg paraldehyde. Blood was examined 5-10 minutes before administration of the drug and 1, 6, 12 and 24 hours after administration. The authors found no trace of the drug in the bloodstream after 24 hours.

4.3. METABOLISM

The available evidence suggests that the majority of the administered paraldehyde is metabolized by the liver (Levine et al., 1939; Hitchcock and Nelson, 1943; Keplinger and Wells, 1957; Breen et al., 1973; Browne, 1983;

Goodman and Gilman, 1970). Zaleska and Gessner (1983a) indicated that the major process responsible for the rapid disappearance of paraldehyde by mice administered ^{14}C -paraldehyde intraperitoneally was its efficient metabolic degradation (~72%) to carbon dioxide and water; acetaldehyde was an intermediate.

Goodman and Gilman (1970), Hitchcock and Nelson (1943) and Sitting (1981) suggested that paraldehyde depolymerizes to acetaldehyde, followed by conversion of acetaldehyde to acetate. Zera and Nagasawa (1981) reported that paraldehyde is metabolized in vitro by the rat hepatic microsomal system to acetaldehyde only in the presence of cytochrome P-450 cofactors. Microsomes from phenobarbital-treated rats resulted in a significantly greater amount of acetaldehyde, while the addition of SKF-525A to the incubation medium competitively inhibited the acetaldehyde generation. Zaleska and Gessner (1983b) reported that pretreatment of mice with phenobarbital enhanced the in vitro generation of acetaldehyde from paraldehyde by mouse liver microsomes 2- to 5-fold. Pretreatment with 3-methylcholanthrene enhanced the production of acetaldehyde by only 0.6-fold. Therefore, cytochrome P-450 mixed function oxidase was involved.

Zaleska and Gessner (1983b) found that the rate of acetaldehyde generation was saturable with the increasing concentration of paraldehyde and that the depolymerization is the rate limiting step in the detoxification of paraldehyde.

Dreisbach (1983) stated that the rate of decomposition of paraldehyde to acetaldehyde does not exceed the rate of acetaldehyde oxidation; therefore, the acetaldehyde does not accumulate in the body.

4.4. EXCRETION

Lang and Borgstedt (1969) reported that 7% of an orally administered dose of paraldehyde was exhaled as parent compound in humans; no other exhaled excretory product was detected. In cats, ~7% of the administered intravenous or intraperitoneal dose was excreted by the lungs within 4 hours (Lang and Borgstedt, 1968). Zaleska and Gessner (1983b) reported that 9.6% of an intraperitoneal dosage administered to mice was excreted in the expired air; the rate of paraldehyde disappearance in mice was rapid, with a biological half-life of ~41 minutes. Levine et al. (1940) reported that up to 28% of an intragastric dose of paraldehyde was excreted unchanged in the expired air of dogs in 36 hours. In none of these studies were other exhaled excretory products detected.

In urine, <3% of the administered paraldehyde was excreted by dogs (Levine et al., 1940) and only 1.24% of the radioactive ^{14}C -paraldehyde was detected in the urine of mice (Zaleska and Gessner, 1983b).

4.5. SUMMARY

Orally administered paraldehyde is rapidly absorbed by the gastrointestinal tract (Osol and Pratt, 1973). In humans, oral administration resulted in 93% absorption (Anthony, 1980).

Paraldehyde is rapidly distributed to the brain within 2-5 seconds after intravenous injection, causing drowsiness (Gardner and Sage, 1941; Robinson, 1938). Paraldehyde can cross the placental barrier (Kotz and Kaufman, 1939; Goodman and Gilman, 1970).

About 70-80% of the administered paraldehyde is metabolized in the liver (Levine et al., 1939; Hitchcock and Nelson, 1943; Keplinger and Wells, 1957; Breen et al., 1973; Browne, 1983; Goodman and Gilman, 1970). In the liver, paraldehyde depolymerizes to acetaldehyde by cytochrome P-450 mixed function

oxidase. Acetaldehyde is then oxidized by aldehyde hydrogenase to acetic acid, which is metabolized to carbon dioxide and water (Hitchcock and Nelson, 1943; Goodman and Gilman, 1970; Zera and Nagasawa, 1981; Zaleska and Gessner, 1983a,b).

The excretion of paraldehyde as parent compound through exhaled air ranges from 7-9.6% in humans, cats and mice (Lang and Borgstedt, 1968, 1969; Levine et al., 1940; Zaleska and Gessner, 1983b) and up to 28% in dogs (Levine et al., 1940). No other exhaled products were detected. Of administered paraldehyde, 3% was detected in the urine of dogs and mice (Levine et al., 1940; Zaleska and Gessner, 1983b).

5. EFFECTS

5.1. CARCINOGENICITY

The only information available regarding the carcinogenicity of paraldehyde is from an initiation-promotion skin-painting study by Row and Salaman (1955). In this study, a solution of 50% paraldehyde in acetone was applied once weekly for 2 weeks at a total dose of 300 mg to the clipped backs of a group of 20 S strain albino male mice. At 4 weeks after the first application, the mice received 18 weekly applications of croton oil. Tumor incidence at the end of the croton oil treatment was 1/18 surviving mice compared with 1/20 croton oil controls. Although no supporting evidence was located, paraldehyde has been designated as a "suspect carcinogen" (NIOSH, 1978).

5.2. MUTAGENICITY

Sasaki and Endo (1978) tested paraldehyde for reverse mutations in Salmonella typhimurium strains TA100 and TA98 in a preincubation assay conducted with and without rat liver S-9 activation. The doses were not reported. Paraldehyde was not reported in this abstract to be mutagenic.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of paraldehyde in laboratory animals could not be located in the available literature as cited in the Appendix. Delayed respiratory movements have been observed in human neonates following therapeutic administration of paraldehyde to the mother during labor (Goodman and Gilman, 1970).

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the other reproductive effects of paraldehyde could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Pertinent data regarding the chronic oral, inhalation or dermal toxicity of paraldehyde in laboratory animals could not be located in the available literature as cited in the Appendix.

In humans, the usual therapeutic oral dose of paraldehyde is 5-10 mL (Goodman and Gilman, 1970). Frequent administration may result in irritation of the mucous membrane, while chronic poisoning may result in acidosis, bleeding gastritis, muscular irritability, azotemia, oliguria, albuminuria, leukocytosis, fatty changes in the liver and kidney, hepatitis, nephrosis, pulmonary hemorrhage and edema and dilation of the right heart. Prolonged use results in tolerance and dependence; withdrawal may result in hallucinations and delirium tremens.

5.6. OTHER RELEVANT INFORMATION

The oral LD₅₀ of paraldehyde is 1.5-1.65 g/kg in rats (Figot et al., 1952; NIOSH, 1985) and 3.33 g/kg in rabbits (NIOSH, 1985). Browne (1983) stated that oral administration of paraldehyde can cause irritation and corrosion of the mouth and stomach and irritation and corrosion of the rectum and large intestine when the compound is given by rectal route. At least 95 cases of death from paraldehyde overdose were reported, and large doses may result in coma, right-sided heart failure and pulmonary edema and hemorrhages (Browne, 1983).

Sleep is induced within 15 minutes at therapeutic oral doses of 4-8 mL, but there is little effect on blood pressure or respiration at these doses (Goodman and Gilman, 1970). At slightly higher doses, symptoms of poisoning, including rapid, labored breathing and markedly depressed blood pressure, ensue. Many manifestations of chronic usage (see Section 5.5.) are also observed with acute poisoning.

According to Goodman and Gilman (1970), deaths have occurred at oral doses of 25-150 g (~25-150 mL). The minimal blood level associated with death is 50 mg % (500 mg/L).

5.7. SUMMARY

Paraldehyde was negative as a tumor initiator when applied to the skin of mice followed by promotion with croton oil (Row and Salaman, 1955). Paraldehyde was also negative in a reverse mutation assay in S. typhimurium strains TA100 and TA98 with and without metabolic activation (Sasaki and Endo, 1978). Pertinent data regarding the teratogenicity and reproductive effects in laboratory animals could not be located in the available literature as cited in the Appendix. Therapeutic administration of paraldehyde to human mothers during labor has resulted in delayed respiratory movements in neonates (Goodman and Gilman, 1970). No chronic or subchronic toxicity studies in laboratory animals were available. Paraldehyde is used therapeutically in humans as a depressant at oral doses of 5-10 mL (~5-10 g) (Goodman and Gilman, 1970). Prolonged use results in tolerance and dependence, acidosis, bleeding gastritis, muscular irritability, fatty changes in the liver and kidney, hepatitis, nephrosis, pulmonary hemorrhage and dilation of the right heart, among other effects. Withdrawal may result in delirium tremens. Deaths have occurred at doses of 25-150 g. At acute doses slightly higher than 8 mL (~8 g), labored breathing and hypotension result. The manifestations of acute poisoning are similar to those of chronic poisoning.

6. AQUATIC TOXICITY

Pertinent data regarding effects of paraldehyde on aquatic biota could not be located in the available literature as cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent guidelines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or food, and ACGIH, NIOSH or OSHA occupational exposure limits could not be located in the available literature as cited in the Appendix.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic biota from the toxic effects of paraldehyde could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Paraldehyde was negative as a tumor initiator when applied to the skin of mice followed by promotion with croton oil (Row and Salaman, 1955). Paraldehyde was also negative in a reverse mutation assay in S. typhimurium strains TA100 and TA98 with and without metabolic activation (Sasaki and Endo, 1978). Pertinent data regarding the teratogenicity and reproductive effects in laboratory animals could not be located in the available literature as cited in the Appendix. Therapeutic administration of paraldehyde to human mothers during labor has resulted in delayed respiratory movements in neonates (Goodman and Gilman, 1970). No chronic or subchronic toxicity studies in laboratory animals were available. Paraldehyde is used therapeutically in humans as a depressant at oral doses of 5-10 mL (~5-10 g) (Goodman and Gilman, 1970). Prolonged use results in tolerance and dependence, acidosis, bleeding gastritis, muscular irritability, fatty changes in the liver and kidney, hepatitis, nephrosis, pulmonary hemorrhage and dilation of the right heart, among other effects. Withdrawal may result in delirium tremens. Deaths have occurred at doses of 25-150 g. At acute doses slightly higher than 10 mL (~10 g), labored breathing and hypotension result. The manifestations of acute poisoning are similar to those of chronic poisoning.

The lack of positive carcinogenicity data and subchronic and chronic toxicity data in animals precludes derivation of a q_1^* or an ADI from animal data. Although short-term therapeutic use of paraldehyde at oral doses of 4 or 5 mL (~4 or 5 g) in humans is considered safe, prolonged use at these doses is associated with frank effects (Goodman and Gilman, 1970). Therefore, an ADI cannot be derived from human data.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

No subchronic or chronic toxicity, teratogenicity or reproduction studies in laboratory animals were available. Paraldehyde has been used therapeutically in humans at oral doses of 4-10 mL (4-10 g). Acute use of these doses are considered safe; however, prolonged usage of therapeutic doses is associated with acidosis, bleeding gastritis, muscular irritability, azotemia, oliguria, albuminuria, leukocytosis, fatty changes in livers and kidneys, hepatitis, nephrosis, pulmonary hemorrhage and edema and dilation of the right heart. The severity of these effects warrants an RV_e of 9. Although these effects are observed with prolonged usage, the duration probably does not approach chronic or lifetime exposure; therefore, an uncertainty factor of 10 must be applied to the dose of 4 g/day resulting in an MED of 0.4 g/day or 400 mg/day. The RV_d is 1.6. Multiplying the RV_d by the RV_e results in a CS of 14.4, which corresponds to an RQ of 1000.

In a previous determination of the RQ, U.S. EPA (1983) stated that the lack of subchronic or chronic dose-response data precluded the derivation of an RQ. The current determination reviews the effects of prolonged therapeutic uses of paraldehyde by humans more thoroughly than did U.S. EPA (1983). Closer examination of the human data, therefore, indicated the data were sufficient to derive an RQ.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Data regarding the carcinogenicity of paraldehyde are limited to that reported by Row and Salaman (1955) (see Section 5.1.). Paraldehyde was negative as a tumor initiator when applied to the skin of mice followed by promotion with croton oil.

Based on the inadequate evidence of carcinogenicity in animals and the lack of evidence in humans, paraldehyde would be classified as a Group 3 chemical according to the IARC classification scheme. Based on U.S. EPA (1984) guidelines for carcinogen risk assessment, unavailability of human cancer data and inadequate evidence of animal carcinogenicity, the overall weight of evidence classification is Group D, meaning paraldehyde cannot be classified as a human carcinogen.

10. REFERENCES

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APPENDIX
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CAS online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1985-1986. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

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Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

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USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.